

## Theory of Coherent and Incoherent Nuclear Spin Dephasing in the Heart

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We present an analytical theory of susceptibility induced nuclear spin dephasing in the capillary network of myocardium. Using a strong collision approach, equations are obtained for the relaxation rate of the free induction and the spin echo decay. Simulation and experimental data are well predicted by the theory. Since paramagnetic deoxyhemoglobin as the origin of nuclear spin dephasing has a higher tissue concentration in myocardium supplied by a stenotic, i.e., significantly narrowed, coronary artery, spin dephasing might serve as a diagnostic tool. Our approach can be modified for capillary networks in other tissues than myocardium and may be applied in material science.

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In cardiology, a paramount goal is the detection of significant narrowing, called stenosis, of coronary arteries, and—even more important—the detection of the associated area of the cardiac muscle. There is evidence that this area can be distinguished from normally supplied tissue without contrast agent by NMR imaging from its different transverse spin relaxation time [1]. Water proton spin dephasing is induced by spin-spin interactions and susceptibility differences between different histological substructures such as intra- and extravascular space. In native tissue, this difference is related to the paramagnetic property of deoxygenated hemoglobin which induces perivascular field gradients. Deoxyhemoglobin, which results from intracapillary deoxygenation of almost 100% oxygenated arterial hemoglobin, is predominately located in the capillary and venous system. In the cardiac muscle, this blood oxygen level dependent (BOLD) effect is almost solely due to the magnetic field inhomogeneities around capillaries since they contain more than 90% of intramyocardial blood volume [2]. In myocardium supplied by a stenotic coronary artery, coronary autoregulation tries to maintain sufficient perfusion by compensatory filling of capillaries (recruitment), i.e., deoxyhemoglobin increases in tissue and spin dephasing is accelerated when compared to normally supplied tissue [1]. This difference of spin dephasing can be pronounced by pharmacological coronary dilation since a higher oxygen supply decreases the tissue concentration of deoxyhemoglobin in normal myocardium [3–5], whereas it does not in the poststenotic myocardium [1].

Though the relation between spin dephasing and coronary microcirculation is of great interest for the diagnosis of coronary artery disease, at present there is no satisfying analytical theory that describes the dephasing of diffusing spins in the inhomogeneous magnetic field of the capillary system. There exist theories on spin dephasing for very long and very short correlation times of diffu-

sion induced magnetic field fluctuations. The assumption of static dephasing of spins as proposed by Yablonski *et al.* [6] is not valid in human cardiac NMR imaging systems (field strength less than 2 T) since the diffusion distance  $l$  during relaxation (relaxation time  $T_2^* > 30$  ms,  $D = 1 \mu\text{m}^2/\text{ms}$ ,  $l > \sqrt{2T_2^*D} \approx 8 \mu\text{m}$ ) has the same magnitude as the intercapillary distance ( $19 \mu\text{m}$ ). Thus, a single nuclear spin experiences almost the whole pericapillary magnetic field gradient during its relaxation. Kiselev and Posse [7] recently proposed analytical treatments for long and short correlation times. The first extends the static dephasing model by including diffusion. However, only the effect of a *linear* local field gradient on relaxation is considered. Application of this approach would be valid if large vessels would dominate the microvascular architecture of myocardium, which is, however, not the case. The other is a perturbation approach in the local fields. In the cardiac muscle, the motional narrowing condition  $\tau\langle\omega^2\rangle^{1/2} \ll 1$  with correlation time  $\tau$  and variance of fluctuations of the local fields (expressed as frequency)  $\langle\omega^2\rangle$  is not fulfilled, though. Approaches which consider spin dephasing for arbitrary correlation times as the Gaussian or Lorentzian phase approximation were not successful since they neither revealed the correct field dependence of the relaxation rate [8] nor the correct fluctuation-dissipation relation [7].

In this paper, an analytical theory is proposed which describes coherent and incoherent spin dephasing in the capillary network of myocardium. It is not an extension of the static dephasing model or a perturbation approach. Instead, it is based on a strong collision approximation which includes both the static dephasing and the motional narrowing regime as two limiting cases.

It has to be emphasized that this approach is not restricted to myocardium, but can be modified for the description of transverse relaxation in capillary networks of other tissues as well. Applications in material science are

possible, too. For example, the effect of complex potentials on spin diffusion, and, hence, on spin dephasing, is exploited to determine the microstructure of spatially or magnetically heterogeneous media [9]. Examples for the former are porous structures, for the latter polymer solutions and liquid crystals in which magnetic heterogeneity is induced by either paramagnetic impurities or an inhomogeneous electrical current. After modifications for the appropriate geometry, the analysis presented below should also be applicable in that field of research.

We will first discuss the *tissue model* employed. The regular parallel architecture of muscle fibers and capillaries in myocardium [10] allows one to reduce considerations from the whole tissue to one tubular capillary (radius  $R_c$ ) which is concentrically surrounded by its mean cylindrical supply region with radius  $R_s$  (Krogh model [11]). Nuclear spin diffusion in the whole tissue is replaced by restricted diffusion in the supply region, i.e., reflectory boundary conditions are introduced at  $R_s$ , and, since the capillary wall is nearly impermeable for water on the time scale of spin dephasing [12], also at  $R_c$ . We consider only relaxation of extracapillary nuclear spins since in myocardium the relative intracapillary blood fraction  $\varsigma = R_c^2/R_s^2$  is less than 10%. The effect of diffusion in field gradients along the capillary axis on spin dephasing is negligible, i.e., it is necessary only to consider two-dimensional diffusion of spins within two concentric circles ( $R_c, R_s$ ). Basic magnetostatics provides the susceptibility related spin frequency shift around the capillary in cylindrical coordinates as

$$\omega(r, \phi) = -\delta\omega R_c^2 \cos(2\phi)/r^2, \quad (1)$$

with the characteristic equatorial frequency shift  $\delta\omega = 2\pi\gamma\Delta\chi B_0 \cos(\theta)$ , where  $\gamma$  is the gyromagnetic ratio,  $\Delta\chi$  is the susceptibility difference, and  $\theta$  is the tilt angle between the capillary axis and the external field which is almost  $90^\circ$  in a clinical scanner. Since  $\Delta\chi < 8 \times 10^{-8}$  for blood, the intracapillary magnetization is less than 1 mG for clinical NMR magnets and  $\delta\omega \leq 168 \text{ rad s}^{-1}$ . The contribution of fields of neighboring capillaries is negligible due to the intercapillary distance of  $19 \mu\text{m}$ .

The starting point of our analytical treatment is the free induction decay of the local nuclear transverse magnetization. The time evolution (polar notation:  $m = m_x - im_y$ ) at  $x = (r, \phi)$  is determined according to the Bloch Torrey diffusion equations [13] which, written in rotating frame coordinates, are

$$\partial_t m(x, t) = [D\nabla^2 + i\omega(x)]m(x, t), \quad (2)$$

with diffusion coefficient  $D$ . The formal solution of Eq. (2) is  $m(x, t) = \exp[[D\nabla^2 + i\omega(x)]t]m(x, 0)$ . Since the spatial resolution of clinical NMR scanners is far above that of capillary dimensions (mm vs  $\mu\text{m}$ ), the observable is the mean transverse magnetization  $M(t)$

within the supply region with volume  $V$ :

$$M(t) = V^{-1} \int_V dx \exp[[D\nabla^2 + i\omega(x)]t]m(x, 0). \quad (3)$$

The homogeneous water concentration in the cardiac muscle implies a homogeneous initial magnetization distribution  $m(x, 0)$  which for simplicity is normalized to  $m(x, 0) = 1$ . Since Eq. (2) cannot be solved analytically when the local frequency is given by Eq. (1), a different approach is necessary.

Let us first consider the *fluctuations* of the local magnetic fields, represented by the corresponding local NMR frequencies  $\omega(x)$  that a diffusing nuclear spin experiences. Their autocorrelation function  $K(t)$  is determined by  $K(t) = V^{-1} \int_V dx \omega(x) \exp(tD\nabla^2)\omega(x)$ , where  $\exp(tD\nabla^2)$  is the Green's function of the restricted diffusion. The *correlation time*  $\tau$  of the field fluctuations is defined as the mean relaxation time [14] of the autocorrelation function,  $\tau = \int_0^\infty dt K(t)/K(0)$ . Using the techniques of Ref. [14], we obtain [15]

$$\tau = (R_c^2/4D) \ln(\varsigma)/(\varsigma - 1). \quad (4)$$

Inserting realistic values of relative intracapillary blood volume ( $\varsigma = 5$  to  $10\%$ ), capillary radius ( $R_c = 2.5$  to  $2.75 \mu\text{m}$ ), and the diffusion coefficient ( $D = 1 \mu\text{m}^2/\text{ms}$ ) into Eq. (4) implies that  $\tau \leq 6 \text{ ms}$ . Relaxation times of the free induction decay observed using clinical scanners are  $T_2^* \geq 30 \text{ ms}$ . Hence, the relaxation time describing the contribution of field inhomogeneities is even longer. This implies that on a time scale in which significant variations of  $M(t)$  occur the local field fluctuations are stochastically independent.

This stochastic independence suggests replacing the diffusion operator  $D\nabla^2$  in Eq. (2) by a *strong collision operator* [16]. This operator describes the diffusion as a stationary Markov process with a single rate  $\lambda$  that governs the relaxation to the steady state distribution  $p(x)$ , independent of the initial state. Because of the homogeneity of water in tissue, the steady state distribution is simply  $p(x) = 1/V$ . The generator  $\mathbf{D}$  of the corresponding Markov process is then

$$\mathbf{D} = \lambda(\mathbf{\Pi} - \text{id}), \quad (5)$$

where  $\mathbf{\Pi}$  denotes the projection operator onto the functional space generated by  $p(x)$ , i.e., the application of this operator on some function  $f(x)$  is  $\mathbf{\Pi}f(x) = V^{-1} \int_V dx f(x)$ . The constant  $\lambda$  is determined self-consistently by requiring that  $\mathbf{D}$  describes correctly the field fluctuations. This implies  $\lambda = \tau^{-1}$  [see Eq. (4)].

Instead of directly solving the time evolution of the magnetization [Eq. (3)] under the strong collision assumption, it is more convenient to consider the Laplace transform:

$$\hat{M}(s) = V^{-1} \int_V dx [s - D\nabla^2 - i\omega(x)]^{-1} m(x, 0). \quad (6)$$

Replacing  $D\nabla^2$  by  $\mathbf{D}$  and utilizing the operator identity  $(A + B)^{-1} = A^{-1} - A^{-1}B(A + B)^{-1}$  we obtain, after some algebra,

$$\hat{M}(s) = (1 + s)[\sqrt{(s + \tau^{-1})^2 + \delta\omega^2\tau^2} + s\sqrt{(s + \tau^{-1})^2 + \delta\omega^2} - \tau^{-1}(1 + s)]^{-1}. \quad (7)$$

$M(t)$  can be obtained from this result to arbitrary accuracy as a multiexponential function  $M(t) \approx \sum_{\nu=1}^N f_{\nu} \exp(-\Gamma_{\nu}t)$ , the parameters determined from (7) using the generalized moment method of [14]. The relaxation time of the free induction process corresponds to the lowest order (mean relaxation time) approximation, which provides the best single-exponential approximation,  $M(t) \approx e^{-t/T_2^*}$ , by setting  $T_2^* = \hat{M}(0)$ . Thus,

$$T_2^* = \frac{\tau(1 + s)}{[\sqrt{1 + (\tau\delta\omega)^2} - 1] + s[\sqrt{1 + (\tau\delta\omega)^2} - 1]}. \quad (8)$$

The free induction decay of magnetization is a result of coherent and incoherent spin dephasing. When instead a *spin echo* experiment is performed, a  $180^\circ$  pulse applied at  $t/2$  reflects the spin phase which eliminates the coherent contribution of spin dephasing at the echo time  $t$ . Time evolution of the local magnetization before the  $180^\circ$  pulse is that of a free induction decay  $m(x, t/2) = \exp[D\nabla^2 + i\omega(x)]t/2 m(x, 0)$ . After the phase reflection which is described by the complex adjoint  $m(x, t/2) \xrightarrow{180^\circ \text{ pulse}} m^*(x, t/2)$ , there is again a free induction decay, i.e., the global magnetization  $M_{SE}(t)$  after the echo time  $t$  is

$$M_{SE}(t) = V^{-1} \int_V dV \exp[D\nabla^2 + i\omega(x)]t/2 \times \exp[D\nabla^2 - i\omega(x)]t/2 m(x, 0). \quad (9)$$

Again replacing  $D\nabla^2$  by  $\mathbf{D}$ , differentiating this relation, and exploiting the structure of the operator  $\mathbf{D}$ , we obtain a general relation between the contribution of solely incoherent spin dephasing on relaxation ( $M_{SE}$ ) and that of coherent and incoherent dephasing ( $M$ ):

$$\partial_t M_{SE}(t) = \frac{1}{\tau} [|M(t/2)|^2 - M_{SE}(t)], \quad (10)$$

which is solved by

$$M_{SE}(t) = \frac{e^{-t/\tau}}{\tau} \left( \tau + \int_0^t d\xi e^{\xi/\tau} |M(\xi/2)|^2 \right). \quad (11)$$

For the free induction decay being given by  $M(t) \approx \sum_{\nu=1}^N f_{\nu} \exp(-\Gamma_{\nu}t)$ , one obtains

$$M_{SE}(t) = \sum_{\mu, \nu=1}^N \frac{f_{\mu} f_{\nu}}{1 - \tau R_{\mu\nu}} (e^{-R_{\mu\nu}t} - \tau R_{\mu\nu} e^{-t/\tau}), \quad (12)$$

where  $R_{\mu\nu} = (\Gamma_{\mu} + \Gamma_{\nu})/2$ .

The determination of the relaxation time  $T_2$  of  $M_{SE}(t)$  depends on the experimental setup. When  $T_2$  is determined from a single echo time  $t$  or a multiecho sequence [17] with an interecho time  $t$ , then  $T_2$  is usually obtained from

$$T_2 = -\ln[M_{SE}(t)]/t. \quad (13)$$

However, since  $M_{SE}(t)$  is *not* single exponential already in the simplest case,  $N = 1$ , the above definition renders  $T_2$  effectively dependent on the echo time  $t$ .

When  $T_2$  is determined from several experiments with varying echo times, the best single-exponential approximation,  $M_{SE}(t) \approx e^{-t/T_2}$ , is required. Within the mean relaxation time approximation,  $T_2 = \int_0^\infty dt M_{SE}(t)/M_{SE}(0)$ , Eq. (12) gives

$$T_2 = T_2^* + \tau. \quad (14)$$

Equations (8) and (14) allow the analysis of various limiting cases. The *motional narrowing* regime is given for  $\tau\langle\omega^2\rangle^{1/2} \ll 1$ . Then, the relaxation rate of the free induction process is  $1/T_2^* = \tau\langle\omega^2(x)\rangle$  with the spatial variance of the spin precession frequency  $\langle\omega^2(x)\rangle = \tau\delta\omega^2/2$ . This relation is the well-known general result for the transverse relaxation rate obtained for the motional narrowing limit.

For very long correlation times, one obtains  $1/T_2^* = 2\tau\delta\omega$  and  $1/T_2 = 0$ , i.e., relaxation is due solely to coherent spin dephasing. For very short correlation times, one obtains  $T_2^* \approx T_2$ , i.e., in this limit the free induction decay is mainly due to incoherent spin dephasing.

Another approximation is possible for small relative intracapillary blood volumes ( $s \ll 1$ ) and in the regime  $\tau\delta\omega \leq 1$ , which is realistic in cardiac tissue. Equation (8) then provides  $1/T_2^* = \tau\delta\omega(\sqrt{1 + (\tau\delta\omega)^2} - 1)$ , i.e., the rate of the free induction decay is proportional to the intracapillary volume.

Kennan and Gore [8] determined relaxation rates from *Monte Carlo simulations* of transverse polarized spins as a function of the diffusion coefficient. In Figs. 1 and 2, their results are compared to our theoretical predictions from Eqs. (8), (12), and (13), using their tissue parameters and  $N = 1$ , which proved to be a sufficient approximation. They demonstrate a close similarity of analytically obtained  $T_2^*$  vs  $D$  and  $T_2$  vs  $D$  curves, and those of simulations. The correct asymptotic behavior for very long and short correlation times, as derived above, is evident in both figures. Also the location of the maximum of the  $T_2$  vs  $D$  curves is congruent. Figure 1 demonstrates, furthermore, that the dependence of  $T_2$  on the echo time is described correctly. Figure 2 exhibits the correct dependence on the capillary radius.

We recently performed  $T_2^*$  mapping in hearts of volunteers [5] before and after application of the coronary dilator dipyridamol, which increases coronary flow by a factor of about 5 without affecting oxygen consumption. This

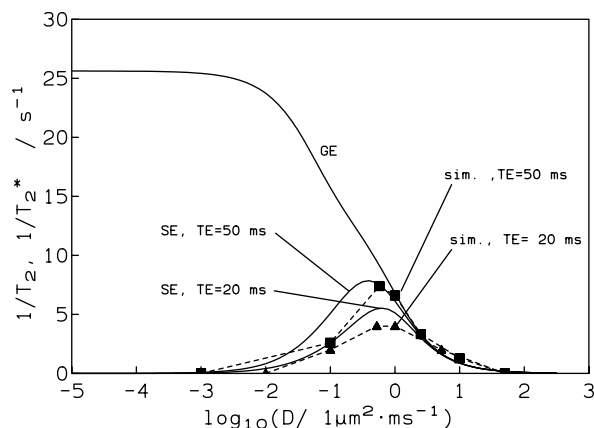


FIG. 1. Relaxation rates of the free induction decay of a gradient echo ( $1/T_2^*$ , GE) and spin echo experiment ( $1/T_2$ , SE) as function of the diffusion coefficient. For comparison with simulation data (sim.), the tissue parameters were obtained from Ref. [8] as relative intracapillary blood volume  $\varsigma = 5\%$ , capillary radius  $R_c = 2.5 \mu\text{m}$ , intracapillary magnetization of  $1.6 \text{ mG}$  ( $\delta\omega = 269 \text{ rad s}^{-1}$ ). The theoretical results (solid lines) were obtained from Eq. (8) for the free induction decay, and from Eqs. (12) and (13) for the spin echo. Two echo (TE) times were analyzed.

decreases the deoxyhemoglobin content and one observes an increase of  $T_2^* \approx 36 \text{ ms}$  by 17%. The theory presented above predicts an increase of 13% to 18%, which is in good agreement with the experimental data.

In summary, we developed an analytical theory for the description of spin dephasing in the inhomogeneous magnetic field of the capillary network of myocardium. The underlying strong collision approach is justified in the

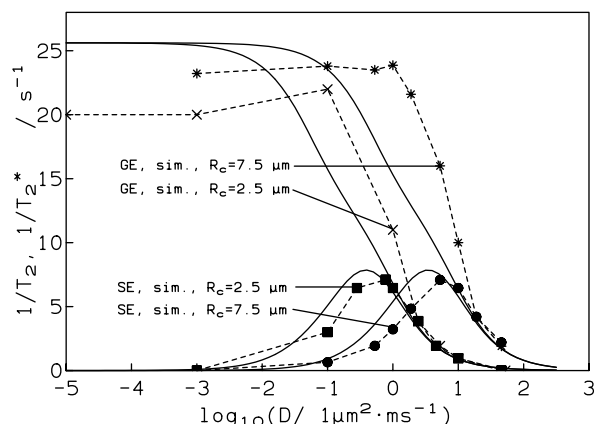


FIG. 2. Relaxation rates of free induction decay ( $1/T_2^*$ , GE) and spin echo experiments ( $1/T_2$ , echo time = 50 ms, SE). Simulation (sim.) and theoretical (solid lines) results are compared for a capillary radius of 2.5 and 7.5  $\mu\text{m}$ . Other parameters are as in Fig. 1.

cardiac muscle and, most probably, albeit with modifications according to different vascular architectures, for many other tissues as well. Note that this approach is not only valid when spin dephasing occurs on a much longer time scale than the local field fluctuations, which is the basis for the strong collision approximation, but also in the static dephasing time.

In our applications, we considered only the single-exponential (mean relaxation time) approximation of the full relaxation curve  $M(t)$ , which proved sufficient for the parameter regime in question. However, in particular for short spin echo times, it can be important to describe the short time behavior of  $M(t)$ , e.g.,  $\frac{d}{dt} M(t)|_{t=0} = 0$ , in more detail. This is readily possible using the multiexponential approximation for  $M(t)$  (see also [18]).

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